Remarks

Entry of the foregoing, reexamination and further and favorable reconsideration of the above-identified application is respectfully requested. By the foregoing amendment, claim 16 has been amended to recite that the method is a method of treating a disease involving chronic pain, epilepsy or deriving from disorders and/or injuries of the motor system. Moreover, new claim 24 has been added and is directed to a method of treating and/or preventing chronic pain or epilepsy. Support for newly added claim 24 may be found in the specification as filed, at the very least, at page 4, lines 18-20; page 5, lines 11-27; and throughout the specification as filed. Finally, claims 18-20 and 22 have been amended to be dependent on claim 16 and newly added claim 24. No new matter enters by way of this amendment.

Restriction Requirement

The Examiner continues to maintain the Restriction Requirement first set forth in the Office Action mailed April 21, 2009. Applicants would again like to reiterate their traversal of this requirement, and incorporate herein their arguments provided in their May 21, 2009, Response to Restriction Requirement.

Rejection of Claims 16, 18-20 and 22 Under 35 U.S.C. § 112, First Paragraph

Claims 16, 18-20 and 22 have been rejected under 35 U.S.C. § 112, first paragraph, for purportedly not being enabled by the specification as filed. For at least the following reasons, withdrawal of this rejection is believed to be in order.

Initially, sodium channel blockers were known, prior to the present invention, to be useful for treating neuropathic pain, chronic pain, neurodegenerative diseases, epilepsy, etc. (*See* the Application as Filed at 1-2). However, sodium channel blockers were also known to possess several side effects, including bradycardia, hypotonia, ataxia, sedation, gastrointestinal disorders, liver damage, etc. (*Id.* at 3-4). The applicants unexpectedly found that by administering a selective serotonin uptake inhibitor simultaneously with a sodium channel blocker, a marked increase in the sodium channel

blocking activity was observed, allowing for lower therapeutic doses of the sodium channel blockers and thus fewer side effects. (*Id.* at 4).

Claim 16 has been amended to recite that the method being claimed is a method of treating a disease in a mammal, wherein said disease involves chronic pain, epilepsy or is derived from disorders and/or injuries of the motor system. The claimed method involves administering a pharmaceutical composition comprising both a sodium channel blocker and a selective serotonin uptake inhibitor. As noted above, sodium channel blockers were known to be effective for treating diseases involving chronic pain, epilepsy, and those diseases derived from disorders and/or injuries of the motor system. Thus, clearly methods of treating diseases involving chronic pain, epilepsy, and those diseases derived from disorders and/or injuries of the motor system, by the administration of a sodium channel blocker were enabled at the time the present application was filed. However, there was a need in the art to reduce the side effects associated with the administration of therapeutic amounts of a sodium channel blocker. The inventors solved this need when they unexpectedly discovered that when a selective serotonin uptake inhibitor is administered together with a sodium channel blocker to treat diseases involving chronic pain, epilepsy, and those diseases derived from disorders and/or injuries of the motor system, a marked increase in the sodium channel blocking activity is achieved. (Application as Filed at 4). Thus, when administered in combination with a selective serotonin uptake inhibitor, the amount of sodium channel blocker needed to obtain a therapeutic effect is lower, allowing for a smaller dose, and this as a result reduces the known side effects associated with its administration.

Therefore, clearly one of skill in the art would have been enabled to practice the claimed methods of treating a disease involving chronic pain, epilepsy, and those diseases derived from disorders and/or injuries of the motor system. The amount of experimentation necessary to practice the claimed invention would be minimal, and would only require one of skill in the art to adjust the known therapeutic dosage of a particular sodium channel blocker to take into account the potentiating effect of the co-administered selective serotonin uptake inhibitor. The applicants have provided sufficient guidance in the specification as to how to determine the therapeutic dosage of a sodium channel blocker when it is co-administered with a selective serotonin uptake

inhibitor. *See*, for example, pages 7-12 of the specification as filed, where the applicants determined the potentiating effect of a selective serotonin uptake inhibitor on the activity of sodium channel blockers (including the reflex inhibitory activity, tremor inhibitory activity, anti-seizure activity, etc.) By determining the potentiating effect of the selective serotonin uptake inhibitor, one of skill in the art would be able to determine, without undue experimentation, how much the dosage of the sodium channel blocker may be lowered so that side effects are avoided, yet a therapeutic effect is still obtained.

Thus, claim 16 (and dependent claims 18-20 and 22) are clearly enabled by the specification as filed.

With respect to newly added claim 24, this claim is directed to methods of treating and/or preventing chronic pain and epileptic seizures. As the Examiner has noted, the specification as filed enables the treatment of chronic pain and epilepsy. (3/17/10 Office Action at 2). The specification also enables the prevention of conditions such as chronic pain and epileptic seizures. The compositions of the present invention comprise sodium channel blockers, which block the voltage-dependent sodium channels and therefore, as the Examiner correctly noted, are useful for treating pain and epileptic seizures. However, in addition to being useful for the treatment of such conditions, the compositions of the claimed invention also prevent further episodes of pain and further epileptic seizures by blocking the voltage-dependent sodium channels. In fact, on page 10 of the specification as filed, the applicants have provided data showing that pre-treatment with selective serotonin uptake inhibitors and sodium channel blockers prior to inducing seizures inhibited the seizures, and thus the compositions of the claimed invention are clearly enabled for preventing epileptic seizures.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-4, 6, 16, 18-20 and 22 Under 35 U.S.C. § 103(a)

Claims 1-4, 6, 16, 18-20 and 22 have also been rejected under 35 U.S.C. § 103(a) for purportedly being obvious over Fitzgerald et al. (2(3) TECHNIQUES IN REGIONAL ANESTHESIA AND PAIN MANAGEMENT 119-129 (1998)) in view of Coe et al. (U.S. Appl. Publ. No. 2001/0036943A1) and further in view of Carbon set al. (U.S. Patent No.

6,191,142). For at least the reasons set forth below, withdrawal of this rejection is believed to be in order.

As discussed in the Amendment and Response dated December 7, 2009, said discussion incorporated herein by reference, Fitzgerald et al. (1) makes no mention of co-administering an anti-convulsant, such as a sodium channel blocker, and an anti-depressant, such as a selective serotonin uptake inhibitor; (2) teaches away from the use of selective serotonin uptake inhibitors with other drugs, due to "significant drug interactions." (Fitzgerald et al. at 122); and (3) determines that with respect to selective serotonin uptake inhibitors (such as fluoxetine, paroxetine, sertraline and venlafaxine) "there is little evidence to support their use in the primary treatment of chronic pain." (*Id.* at 121). Thus, Fitzgerald et al. would not have motivated one of skill in the art to use a selective serotonin uptake inhibitor in a composition to be used to treat chronic pain, and in fact teaches away from the use of a selective serotonin uptake inhibitor to treat chronic pain and also teaches away from combination therapies using a selective serotonin uptake inhibitor and any drug (including sodium channel blockers).

Neither of the references cited by the Examiner cure the deficiencies of Fitzgerald et al. nor would have motivated one of skill in the art to make the claimed compositions and use them in the claimed methods. Specifically, Coe et al. discloses a pharmaceutical composition for the treatment of acute, chronic and/or neuropathic pain and migraines, wherein the composition comprises a nicotine receptor partial agonist, an analgesic agent and a pharmaceutically acceptable carrier. (Coe et al. at ¶ 0004). Coe et al. provides a long list of possible analgesics that could be used in their disclosed composition, and includes selective serotonin uptake inhibitors in this list. (*Id.* at ¶¶ 0006 and 0138). Also included in the list of possible "analgesics" are tricyclic anti-depressants, anti-histamines, caffeine and steroids. (*Id.* at ¶ 0138). However, Coe et al. provides no data showing that any of their claimed compositions are effective for treating acute, chronic and/or neuropathic pain, let alone data showing that the co-administration of a nicotine receptor partial agonist and a selective serotonin reuptake inhibitor is more effective for treating acute, chronic and/or neuropathic pain than either the administration of nicotine receptor partial agonist or a selective serotonin uptake inhibitor alone. Coe et al. merely discusses biological assays that could be used to determine the compositions effect on pain. (*Id.* at

¶¶ 0285-0297). Moreover, in view of the teachings of Fitzgerald et al. that "there is little evidence to support [the use of selective serotonin reuptake inhibitors] in the primary treatment of chronic pain" (Fitzgerald et al. at 121) and the teachings of Waldman et al. (previously cited by the Examiner) that selective serotonin uptake inhibitors do not appear to be as efficacious as tricyclic anti-depressants for the treatment of neuropathic pain, one of skill in the art would have had no motivation to select a selective serotonin uptake inhibitor from the long list of possible purported "analgesics," which includes analgesics such as opioid analgesics, COX 1 inhibitors, anesthetic agents, etc., as well as tricyclic anti-depressants (which, as noted by Waldman et al., were long known to be useful for treating neuropathic pain (Waldman et al. at 60)).

Carson et al. is merely cited by the Examiner as purportedly teaching that neuropathic pain is a chronic pain condition. Carson et al. teaches compositions for the treatment of neuropathic pain that comprise an aroyl aminoacyl pyrrole. (Carson et al. at col. 2, line 52 – col. 3, line 35). Carson et al. makes no mention of the use of a selective serotonin uptake inhibitor in a composition for treating neuropathic pain.

Therefore, none of the references cited by the Examiner disclose or suggest treating chronic pain by administering in combination a sodium channel blocker and a selective serotonin uptake inhibitor. Even if the teachings of Fitzgerald et al. and Coe et al. were combined, at most one of skill in the art would have been motivated to treat neuropathic pain in a patient by administering a composition comprising a nicotine receptor partial agonist and lamotrigine, because Coe et al. states that a sodium channel blocker is a possible analgesic that could be used together with a nicotine receptor partial agonist in their disclosed compositions, and Fitzgerald et al. teaches that lamotrigine (a sodium channel blocker) is indicated for the treatment of neuropathic pain. Moreover, if one of skill in the art were motivated to combine drugs known to be useful for treating chronic pain, one of skill in the art would have used drugs having different mechanisms of action that were known to be highly effective for such a treatment so that the effective amounts of the drugs used in combination would be less than the effective amounts used individually, thus reducing known side effects (such as CNS-related toxicity associated with lamotrigine). Thus, one of skill in the art at most would look towards combining two drugs known to be highly effective for treating chronic pain, but from different

classes (and therefore that work by different mechanisms), such as an anti-convulsant and a tricyclic anti-depressant, or perhaps a nicotine receptor partial agonist and an anti-convulsant, such as a sodium channel blocker.

One of skill in the art, however, would not have been motivated to administer to a patient for the treatment of chronic pain a combination of an anti-convulsant, such as a sodium channel blocker, and a selective serotonin uptake inhibitor. In fact, one of skill in the art, given the "minimal" effect a selective serotonin uptake inhibitor has on chronic pain (*see* Fitzgerald et al. and Waldman et al.), would have expected that when administered in combination with a sodium channel blocker, the amount of a sodium channel blocker needed to be effective for treating chronic pain would be the same as if the sodium channel blocker were administered alone. Therefore, one of skill in the art would not have been motivated to administer a sodium channel blocker and a selective serotonin uptake inhibitor together, as one of skill in the art would have expected that there would be no reduction in the known side effects of sodium channel blockers, or even an improvement in therapeutic efficacy.

Thus, even taken together, Fitzgerald et al., Coe et al. and Carson et al. fail to teach or even suggest a pharmaceutical composition comprising a combination of a sodium channel blocker and a serotonin uptake inhibitor, let alone a method of treating chronic pain by administering to a patient such a pharmaceutical composition. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. For this reason alone, the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Finally, as discussed in more detail in the Amendment and Response filed December 7, 2009, and incorporated herein by reference, even if the Examiner had established a *prima facie* case of obviousness, the surprising and unexpected results obtained by the applicants (unexpected and marked increase in the sodium channel blocking activity and a reduction in side effects) would overcome such a *prima facie* case.

In light of these remarks, withdrawal of this rejection under 35 U.S.C. § 103(a) is in order, and the applicants respectfully request the same.

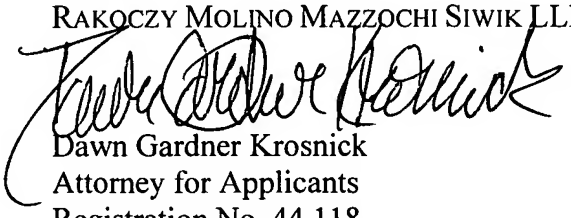
Conclusion

Examination and further and favorable reconsideration of this Application is respectfully requested.

Applicants believe that the present Application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP



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